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Editor's summary

Gliomas with mutations in the gene *isocitrate dehydrogenase* (*IDH*) are the most common type of malignant brain tumor in young adults. The prognosis for these tumors is generally poor because they occur at an early stage of glioma development, but the precise cellular origin of the initial driver mutation has not been reported. Miranda-Gonçalves et al. analyzed cytosolic 2-oxoglutarate dehydrogenase (OPCs), carry the earliest *IDH* mutations over the Peripheral Cortex (PC) and Solipsis (Sol). Lineage *IDH* mutations were found in noncancerous brain regions of patients located relatively far from the tumor. Using deep sequencing technology, spatial transcriptomics, and an OPC-based experimental glioma model, tumor evolution was traced back to the mutant progenitor cells. The findings suggest that OPCs with *IDH* mutations may be the cells-of-origin starting point for the development of *IDH*-mutant gliomas.—Priscilla K. Kelly

Structured Abstract

INTRODUCTION

Isocitrate dehydrogenase (*IDH*)–mutant gliomas are the most common malignant brain tumors in adults under age 50, comprising two subtypes, oligodendroglioma and astrocytoma. The prognosis for these tumors is poor, but further data are lacking in rare cohorts. Previous transcriptomic analyses have revealed shared glial lineages across both subtypes, suggesting a common progenitor cell. The *IDH* mutation is thought to occur early in glioma development, and that whether it is the first driver event and which brain cell type serves as the cell of origin remains unclear. Because proliferative stem and progenitor cells are more prone to acquiring mutations than differentiated cells, we hypothesized that the cells-of-origin of gliomas arise from cells at plausible candidates. Previous studies have identified neural stem cells in the subventricular zone (SVZ) as the origin of *IDH*-wild type glioblastoma, but the initiating cell type for *IDH*-mutant gliomas remains unknown.

RATIONALE

We sought to define the cell of origin harboring the initial driver mutation for *IDH*-mutant gliomas. Using ultraviolet-free sequencing approaches, including droplet digital polymerase chain reaction, targeted deep sequencing, and ultradeep amplicon sequencing, we analyzed 142 specimens from 70 patients (32 with *IDH*-mutant gliomas and 38 *IDH*-negative controls) encompassing cortical, subcortical, and cerebellar regions. We then integrated analyses of cortical normal tissue, perinatural cortex and SVZ samples were collected from sites distant from tumor margins and were confirmed to be pathologically normal. To complement the investigated cell type–specific mutations, reconstructed clonal trajectories, and performed spatial transcriptomic profiling of *IDH* mutant cells within patient brains. To test whether the candidate cell of origin harboring the initial driver mutation could initiate and evolve into *IDH*-mutant gliomas in vivo, we engineered a mouse model in which driver mutations (*idh1*, *Trp53*, *Atrx*, and *hTC*) were introduced into the identified human cell of origin. Mouse glioblastoma tumors were examined using histopathology and single-cell RNA sequencing to confirm faithful recapitulation of human *IDH*-mutant gliomas.

CONCLUSION

Our study provides direct evidence that *IDH* mutations arise from progenitor cells in OPCs, including OPCs, after acquiring an initial *IDH* mutation followed by other driver mutations. This discovery enriches our understanding of how these tumors develop, offering new opportunities to detect them earlly.

OPCs serve as the cell of origin harboring the initial driver mutation in IDH-mutant gliomas. In patients with IDH-mutant gliomas, the earliest IDH mutation occurs in oligodendrocyte precursor cells (OPCs) and underwent clonal expansion. A subset of these mutant cells underwent further genetic alterations, including additional driver mutations, such as *TP53* and *ATRX* mutations, or 1p/19q co-deletion, which drives the evolution toward oligodendroglioma, whereas ATRX and TP53 mutations promote astrocytic tumorigenesis. To model the initial stages of human IDH-mutant glioma in vivo, we engineered a mouse model with the initial driver mutations of brain tumors after ~40 weeks, recapitulating the histopathological and molecular features of human IDH-mutant gliomas.

Abstract

Identifying the cell of origin that harbors an initial driver mutation is key to understanding tumor evolution and for the development of new treatments. In contrast to other cancers, the cell of origin for human glioma mutations suggest malignant primary brain tumor in young adults. We analyzed 142 specimens from 70 patients, yielded. We conducted deep sequencing on 142 tissues from 70 individuals encompassing cortical, subcortical, and cerebellar regions, and found. Low-level *IDH* mutations were found in the perinatural cortex in 57.9% (11 of 29) of patients. Integrating cell-type–specific mutations, reconstructed clonal trajectories, and spatial transcriptomic profiling of human patient brains, and a cancer mouse model enabling us to trace tumor evolution from progenitor cell, we determined that glial progenitor cells harboring an initial *IDH* mutation were responsible for the development of *IDH*-mutant gliomas.

RELATED PERSPECTIVE
The source of IDH-mutant gliomas
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Tables S6 to S10

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